In the Specification:

On page 1, please delete the first paragraph at lines 5-10 and replace with the following paragraph:

This application is a continuation of abandoned Application Serial No. 08/758,005, filed November 27, 1996, which is a continuation-in-part of abandoned Patent Application Serial No. 08/709,910, filed September 9, 1996, which is a continuation-in-part of issued Patent Application Serial No. 08/328,520, filed October 25, 1994, Patent No. 5,591,721, issued January 7, 1997.

On page 5, please delete the first paragraph at lines 1-25 and replace with the following paragraph:

Several preliminary studies on this topic have been published. Agrawal et al. *(Proc. Natl. Acad. Sci. (USA)* (1991) **88:**7595-7599) describes the intravenous and intraperitoneal administration to mice of a 20mer phosphorothioate linked-oligonucleotide. In this study, approximately 30% of the administered dose was excreted in the urine over the first 24 hours with accumulation preferentially in the liver and kidney. Plasma half-lives ranged from about 1 hour ($t_{1/2\alpha}$) and 40 hours ($t_{1/2\beta}$), respectively. Similar results have been reported in subsequent studies (Iversen (1991) *Anti-Cancer Drug Design* **6:**531-538; Iversen (1994) *Antisense Res. Devel.* **4:**43-52; and Sands (1994) *Mol. Pharm.* **45:**932-943). However, stability problems may exist when oligonucleotides are administered intravenously and intraperitoneally. More recently, Agrawal et al. reported that oligonucleotide hybrids containing 2'-O-methyl ribonucleotides at both the 3'- and 5' ends and deoxyribonucleotide

A 2 cont'd

phosphorothioates in the interior portion were absorbed through the gastrointestinal (GI) tract of rats (*Biochem. Pharm.* (1995) **50**:571-576).

Please delete the last paragraph at page 7, line 31 to page 8, line 12 and replace it with the following paragraph:

A 3

The term "non-phosphodiester-linkages" as used herein refers to a synthetic covalent attachment between the 5' end of one nucleotide and the 3' end of another nucleotide in which the 5' nucleotide phosphate has been replaced with any number of chemical groups. Preferable synthetic linkages include alkylphosphonates, phosphorothioates, phosphorodithioates, alkylphosphonothioates, phosphoramidates, phosphoramidites, phosphate esters, carbamates, carbonates, phosphate triesters, acetamidate, and carboxymethyl esters. In one preferred embodiment of the invention, all of the nucleotides of the oligonucleotide are linked via phosphorothioate and/or phosphorodithioate linkages.

On page 9, please delete the third paragraph at lines 15-28 and replace it with the following paragraph:

A 4

For purposes of the invention, the term "2'-substituted oligonucleotide" refers to an oligonucleotide having a sugar attached to a chemical group other than a hydroxyl group at its 2' position. The 2'-OH of the ribose molecule can be substituted with -O-lower alkyl containing 1-6 carbon atoms, aryl or substituted aryl or allyl having 2-6 carbon atoms, e.g., 2'-O-allyl, 2'-O-aryl, 2'-O-alkyl (such as a 2'-O-methyl), 2'-halo, or 2'-amino, but not with 2'-H, wherein allyl, aryl, or alkyl groups may be unsubstituted or substituted, e.g., with halo, hydroxy, trifluoromethyl, cyano, nitro, acyl, acyloxy, alkoxy, carboxyl, carbalkoxyl or amino groups.

Please delete the last paragraph at page 9, line 30 to page 10, line 22, and replace it with the following paragraph:

In one preferred embodiment of the invention, the oligonucleotide administered includes at least one 2'-substituted ribonucleotide at its 3' terminus. In some embodiments, all but four or five nucleotides at its 5' terminus are 2'-substituted ribonucleotides, and in some embodiments, these four or five unsubstituted 5' nucleotides are deoxyribonucleotides. In other embodiments, the oligonucleotide has at least one 2'-substituted ribonucleotide at both its 3' and 5' termini, and in yet other embodiments, the oligonucleotide is composed of 2'-substituted ribonucleotides in all positions with the exception of at least four or five contiguous deoxyribonucleotide nucleotides in any interior position. Another aspect of the invention includes the administration of an oligonucleotide composed of nucleotides that are all 2'-substituted ribonucleotides. Particular embodiments include oligonucleotides having a 2'-O-alkyl-ribonucleotide such as a 2'-O-methyl. Other embodiments include the administration of chimeric oligonucleotides. In one preferred embodiment, the chimeric oligonucleotide has at least one alkylphosphonate internucleotide linkage at both its 3' and 5' ends and having phosphorothioate internucleotide linkages.

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On page 11, please delete the second paragraph at lines 15-17 and replace it with the following paragraph:

In another embodiment, the oligonucleotide is complementary to a gene encoding a protein associated with Alzheimer's disease.

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On page 12, please delete the second paragraph at lines 10-14 and replace it with the following paragraph:

A7

FIG. 1 is a graphic representation showing the time course of radiolabelled oligonucleotide in liver, kidney and plasma following the oral administration of radiolabelled phosphorothioate (PS) oligonucleotide 11 (SEQ ID NO:10);

On page 19, please delete the third paragraph at lines 17-32 and replace it with the following paragraph:

A8

The oligonucleotides administered to the animal may be hybrid oligonucleotides in that they contain both deoxyribonucleotides and at least one 2' substituted ribonucleotide. For purposes of the invention, the term "2'-substituted" means substitution at the 2' position of the ribose with, e.g., a -O-lower alkyl containing 1-6 carbon atoms, aryl or substituted aryl or allyl having 2-6 carbon atoms e.g., 2'-O-allyl, 2'-O-aryl, 2'-O-alkyl, 2'-halo, or 2'-amino, but not with 2'-H, wherein allyl, aryl, or alkyl groups may be unsubstituted or substituted, e.g., with halo, hydroxy, trifluoromethyl, cyano, nitro, acyl, acyloxy, alkoxy, carboxyl, carbalkoxyl or amino groups. Useful substituted ribonucleotides are 2'-O-alkyls such as 2'-O-methyl.

Please delete the last paragraph at page 35, line 32 to page 36, line 18 and replace it with the following paragraph:

A9

The chemical form of radioactivity in rat plasma was further evaluated by HPLC as shown in FIG. 4A and 4B, demonstrating the presence of both intact PS oligonucleotide (A) as well as metabolites (B) 12 hours after oral administration (see FIG. 4B). Intact oligonucleotide was also detected in rat liver 6 hours (FIG. 5B) and 12 hours (FIG. 5C) after oral administration.

Radioactivity in rat brain, thymus, heart, lung, liver, kidney, adrenals, stomach, small intestine, large intestine, skeletal muscle, testes, thyroid, epidermis, whole eye, and bone marrow was detectable 48 hours after oral administration of the radiolabelled oligonucleotide. For unmodified oligonucleotide, minimal intact form was detectable in rat tissue samples. However, as shown in FIG. 11A for the hybrid oligonucleotide and in FIG. 11B for the chimeric oligonucleotide, intact oligonucleotides were detected in plasma and tissue samples of the liver, kidney, spleen, heart, and lung.

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On page 38, please delete the second paragraph at lines 20-26 and replace it with the following paragraph:

A10

Oral absorption of oligonucleotides in fasting animals was also determined with PS- oligonucleotide and hybrid oligonucleotide. Decreased absorption rates were found, indicating that the retention time of the oligonucleotides in the gastrointestinal tract in the fasting animals may be lower than in non-fasting animals.

On page 39, please delete the last paragraph at lines 21-31 and replace it with the following paragraph:

A11

An unmodified HIV-specific 25mer oligonucleotide and hybrid 25mer phosphorothioate-linked oligonucleotide having SEQ ID NO:10 and containing 2'-O-methyl ribonucleotide 3' and 5' sequences and a deoxyribonucleotide interior, as well as two hybrid 18mer phosphorothioate-linked oligonucleotides having SEQ ID NOS:20 and 21, and containing 2'-O-methyl ribonucleotide 3' and 5' sequences and a deoxyribonucleotide interior, were synthesized, purified, and analyzed as follows.